CHRONIC TOXICITY SUMMARY

FLUORIDES including HYDROGEN FLUORIDE

(hydrofluoric acid (aqueous solution); hydrogen fluoride (as a gas); fluoride salts (particulates or in solution))

CAS Registry Number: 7664-39-3

I. Chronic Toxicity Summary

Inhalation reference exposure level	**14 μg HF/m^3** (17 ppb); **13 μg F/m^3**
Oral reference exposure level	**0.04 mg/kg-day**
Critical effect(s)	Skeletal fluorosis
Hazard index target(s)	Bone and teeth; respiratory system

II. Physical and Chemical Properties of HF (HSDB, 1995; CRC, 1994)

Description	Colorless gas (HF), or as particulates
Molecular formula	HF
Molecular weight	20.0 g/mol
Density	0.83 g/L @ 25°C
Boiling point	19.54°C
Melting point	–83.1°C
Vapor pressure	400 torr @ 2.5°C
Solubility	Soluble in water and alcohol
Conversion factor	1 ppm = 0.83 mg/m^3 @ 25°C

III. Major Uses or Sources

Hydrofluoric acid (HF) is a colorless, fuming liquid with a sharp, penetrating odor (Fairhall, 1949). This acid is used in the glass etching, electronic, microelectronic, and petroleum refining and chemical industries (Bertolini, 1992). These industries use HF in the manufacture of such things as computer chips (an important industry in California), phosphate fertilizer, metal cans, plastics, refrigerant chemicals (fluorocarbons), inorganic chemicals, soaps and detergents, high-octane gasoline, and aircraft parts (Wohlslagel *et al.*, 1976; Wing *et al.*, 1991). HF is also used in commercial rust removal products. Another high profile use of HF in California has been as a catalyst in petroleum alkylation to make high-octane gasoline. HF is also a product of combustion of any F containing materials; as such, it is produced during structural fires.

Sodium fluoride has been used as a topical and ingested anticaries agent due to its ability to harden tooth enamel during development. The optimal doses are not well established, but have been suggested to be approximately 0.080 mg/kg/day for 7 to 9 month old infants decreasing to 0.034 mg/kg/day at 13 years of age (Shulman *et al*., 1995). A dose of 1.0 mg F ingested per day was reported to reduce dental caries 43%, and to be associated with a greatly increased rate of minor tooth mottling which caused no esthetic damage (Van Nieuwenhuysen and D'Hoore, 1992). Many communities in California routinely add fluoride to the drinking water. The California Department of Health Services has adopted regulations that establish standards for the addition of F (CDHS, 2002). Any public water system using fluoridation must maintain F levels within the range established for its climate. The ranges vary according to average air temperatures, since people in cooler climates typically drink less water per day than people in warmer climates. Thus, in cooler areas, more F is required to provide the same dental benefit. For 2001-2002, F levels in San Francisco municipal water ranged from 0.65 to 1.1 ppm, while in Los Angeles the range was 0.44 to 0.83 ppm (CDHS, 2002).

The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 48,221 pounds of fluorides and compounds, and 62,670 pounds of hydrogen fluoride (CARB, 2000).

IV. Effects of Human Exposure

The chronic exposure to fluorides, including HF, and the incidence of minimal osseous changes were studied in the workplace by Derryberry *et al.* (1963). In this study, the 8-hour time-weighted average fluoride exposure was calculated for the employment period of each of 74 male workers (30 Caucasian, 44 African-American). The overall average fluoride exposure in these workers was measured as a time-weighted average of 2.81 mg F/m^3. In comparison, the 17 workers within this group who had evidence of minimally increased bone density had an average fluoride exposure of 3.38 mg F/m^3. The other workers were exposed to an average measured concentration of 2.64 mg F/m^3. In addition, urinary fluoride levels were greater in the 17 individuals with greatest exposure compared to the remaining 57 workers (average = 5.18 mg F/L vs. 4.53 mg F/L). No differences between exposed and unexposed individuals were observed for gastrointestinal, cardiovascular, or hematologic systems, or in a physical exam. A statistically significant ($p < 0.05$) increase in the incidence of acute respiratory disease as determined from past medical histories was observed in fluoride-exposed individuals (19/74 vs. 8/67 in controls); radiographic examination revealed a difference of lesser significance ($p < 0.10$) for pulmonary changes (11/74 vs. 4/67). No pulmonary function tests were reported.

An analysis of these data by OEHHA (see derivation section below) showed a statistically significant relationship between air fluoride and the minimal bone density increases. The raw data from the Derryberry *et al.* (1963) study are shown in Table 1. A Pearson correlation matrix of the variables measured in the Derryberry *et al.* study indicated that bone density was best correlated with mean air fluoride level, and to a lesser extent with the age of the individual. A log-logistic regression using the log air fluoride concentration as the independent variable showed a significant ($p < 0.033$) relationship between increasing air

fluoride concentrations and probability of skeletal fluorosis. The parameters for the regression were $\beta_0 = -2.3468$ (std. error = 0.6462), and $\beta_1 = 1.1736$ (std error = 0.5508); the odds ratio for the occurrence of skeletal fluorosis was 3.24. Years of exposure were not correlated with increased bone-density, according to a Pearson Correlation procedure ($p = 0.63$). Bone density has been shown to decrease with age after the age of 40 among normal, non-fluoride-exposed males (Runge *et al*., 1979). As expected, age was very highly correlated with years exposed ($p<0.00001$). Therefore including years exposed in the dose-metric likely introduces a confounding variable (see discussion in Section VI.). In addition, Runge *et al*. (1979) found no association between years exposed and mineral content or bone width among 245 aluminum smelter workers exposed to 2.75 or 3.2 mg F/m^3. For these reasons, years exposed were not used as the dose-metric for bone-density in this analysis.

Although a threshold was not readily apparent from the logistic regression model, grouping the 74 individuals by air fluoride exposure level into quintiles of 15 each with one group of 14, allowed for a comparison of group mean responses (Table 2). The 14 employees exposed to a time-weighted average concentration of 1.07 mg F/m^3 did not exhibit bone density changes. An analysis of the grouped responses using a binomial distribution showed a probability of $p = 0.008$ for obtaining 4/15 increased bone density observations in the 2.34 mg/m^3 group, and a probability of $p = 0.047$ for obtaining 3/15 positive observations in the 1.89 mg F/m^3 group. The 1.89 mg F/m^3 group was therefore considered a LOAEL for chronic skeletal fluorosis, and the 1.07 mg/m^3 group was considered a NOAEL. The above probabilities assume that a chance occurrence is, at most, 1 in 18 of skeletal fluorosis or other cause leading to an abnormally dense x-ray in the general population. Since osteosclerosis is a rare condition that is associated with several types of hematological malignancies such as myeloid leukemia, the actual incidence of conditions leading to osteosclerosis is far below 1 in 18. This lends strong support to the consideration of 1.89 mg/m^3 as a LOAEL for skeletal fluorosis.

Table 1. Data on worker exposure to fluoride from Derryberry *et al.* (1963)

Obser-vation #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg/m^3)	*OEHHA exposure grouping*
1	119	normal	18.5	43.0	2.8	14.7	58	8.16	5
2	0	normal	8.4	24.7	5.3	9.6	42	3.19	4
3	41	normal	15.8	35.0	2.5	9.1	35	3.29	4
4	147	minimally increased	9.6	17.1	2.1	8.9	60	5.98	5
5	120	normal	16.7	20.5	3.4	8.6	55	3.29	4
6	54	minimally increased	17.0	44.0	4.0	8.6	56	7.73	5
7	148	normal	10.5	14.0	3.7	8.4	41	8.32	5
8	314	minimally increased	14.4	22.7	1.7	8.3	56	3.24	4
9	29	normal	17.0	18.2	2.5	7.7	50	2.60	3
10	14	normal	14.3	19.4	2.1	6.3	46	2.33	3
11	115	normal	15.2	18.5	1.4	6.3	38	2.11	3
12	10	minimally increased	10.3	22.0	2.3	6.1	38	2.72	4
13	4	minimally increased	7.1	7.7	2.0	5.7	54	3.22	4
14	51	normal	14.9	42.0	0.8	5.6	46	3.18	4
15	94	normal	16.2	15.4	3.3	5.5	56	5.12	5
16	217	normal	7.1	7.1	2.6	5.3	42	2.54	3
17	281	minimally increased	7.8	8.6	1.1	5.2	36	3.79	4
18	114	normal	10.4	13.2	2.8	5.2	38	7.66	5
19	7	normal	7.8	9.1	2.2	5.1	43	2.91	4
20	308	normal	11.9	6.7	3.5	5.1	44	1.89	2
21	301	minimally increased	15.2	9.5	2.5	5	36	2.56	3
22	72	normal	25.9	13.7	2.1	4.9	55	5.55	5
23	241	minimally increased	17.0	10.0	1.9	4.9	46	4.48	5
24	345	normal	10.5	7.1	2.0	4.9	47	1.49	1
25	26	normal	16.4	12.2	0.5	4.7	39	2.41	3
26	231	minimally increased	16.3	8.2	2.8	4.6	62	1.88	2
27	2	normal	24.7	8.9	2.1	4.6	46	3.53	4
28	295	normal	14.5	10.7	0.9	4.6	44	2.07	3
29	1	normal	8.9	5.9	2.4	4.5	30	1.92	2
30	203	minimally increased	18.2	6.8	1.6	4.4	43	2.66	3
31	63	normal	16.2	7.4	2.0	4.3	55	3.90	5
32	5	normal	4.5	11.5	1.9	4.3	43	1.12	1
33	460	normal	12.5	6.1	1.6	4.3	60	2.13	3

Obser-vation #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg F/m^3)	*OEHHA exposure grouping*
34	249	minimally increased	15.0	8.0	1.8	4.3	39	2.95	4
35	3	normal	7.6	14.5	2.1	4.3	31	3.90	5
36	322	normal	9.3	6.3	2.0	4.3	35	4.23	5
37	8	minimally increased	24.8	5.9	3.0	4.2	55	2.50	3
38	3	normal	15.2	12.2	2.1	4.2	42	1.14	1
39	309	normal	12.1	5.5	2.4	4.1	42	1.94	2
40	36	normal	9.1	13.2	0.8	4.1	33	1.94	2
41	45	normal	11.3	14.0	2.2	4.1	33	3.84	4
42	70	normal	17.9	8.0	1.0	3.9	44	4.00	5
43	250	minimally increased	9.8	6.7	1.5	3.9	35	1.78	2
44	38	normal	16.9	5.9	1.0	3.9	35	2.10	3
45	200	minimally increased	14.0	7.0	2.8	3.8	66	3.92	5
46	183	normal	9.8	4.9	2.2	3.7	48	1.67	2
47	32	normal	12.5	6.6	0.9	3.7	47	2.21	3
48	25	normal	13.6	5.5	1.5	3.7	44	1.86	2
49	21	normal	13.9	9.1	0.4	3.7	50	1.98	2
50	304	normal	13.4	5.0	2.1	3.7	36	2.62	3
51	132	normal	10.9	5.1	2.4	3.6	39	1.81	2
52	6	minimally increased	8.4	4.8	0.9	3.6	35	3.85	5
53	244	normal	16.6	7.1	1.4	3.6	62	2.87	4
54	30	normal	14.0	14.0	0.9	3.6	43	1.56	1
55	88	minimally increased	15.5	4.9	1.7	3.5	66	2.06	2
56	227	normal	16.6	5.7	1.0	3.5	41	1.18	1
57	271	normal	17.7	4.1	3.0	3.4	60	1.82	2
58	19	normal	13.9	10.0	1.8	3.4	41	1.32	1
59	190	normal	9.3	7.7	1.9	3.3	36	1.95	2
60	258	normal	17.8	5.6	1.6	3.2	58	0.87	1
61	278	normal	10.0	7.0	0.3	3.2	34	1.93	2
62	331	normal	12.8	5.6	1.5	3.1	34	1.23	1
63	91	normal	25.3	7.9	0.2	3.1	63	3.49	4
64	342	normal	18.5	6.0	1.3	3	40	2.73	4
65	261	normal	18.1	5.3	0.9	2.9	52	4.41	5
66	291	normal	13.5	4.5	1.5	2.8	34	2.14	3
67	149	normal	11.3	4.5	2.1	2.8	34	0.76	1
68	2	normal	24.7	4.5	1.5	2.7	51	1.15	1
69	4	normal	16.8	5.7	1.2	2.7	56	0.71	1
70	109	normal	8.3	5.1	0.8	2.7	36	1.89	2
71	242	normal	18.1	4.1	1.2	2.5	49	1.26	1

Obser-vation #	ID	Bone density	Years exposed	Urine max F (mg F/L)	Urine min F (mg F/L)	Mean urinary F (mg F/L)	Age (years)	Air fluoride (mg F/m^3)	*OEHHA exposure grouping*
72	179	normal	18.9	3.9	1.0	2.4	46	0.50	1
73	325	minimally increased	11.8	5.0	0.5	2.2	40	2.10	3
74	159	normal	18.9	5.0	0.7	2.1	45	0.67	1

Table 2. Grouped mean exposure

Exposure group	Mean age ± SD	Mean air level mg F/m^3 ± SD	Number of responses	Probability of difference from group 1*
1	45.0 ± 7.0	1.07 ± 0.32	0/14**	Not Applicable
2	43.9 ± 11.2	1.89 ± 0.09	3/15***	0.047
3	43.0 ± 7.6	2.34 ± 0.23	4/15	0.008
4	45.9 ± 9.8	3.22 ± 0.35	5/15	0.001
5	48.5 ± 10.7	5.41 ± 1.72	5/15	0.001

* Probability of obtaining result assuming a chance occurrence of abnormally dense x-ray of, at most, 1 in 18 individuals, using a binomial distribution (Systat for Windows v.5.05, 1994).
** NOAEL
*** LOAEL ($p < 0.05$)

Largent *et al.* (1951) found a significant increase in bone density in the lower thoracic spine, with calcification extending into the lateral ligaments of 3 workers exposed for 17, 14, and 10 years to HF (concentrations not estimated).

A group of 74 men, who were occupationally exposed to unspecified concentrations of HF for an average of 2.7 years, reported occasions of upper respiratory irritation (Evans, 1940). Repeated chest X-rays over a 5-year period did not reveal any visible evidence of lung changes. The death rate of these workers from pneumonia and other pulmonary infections was the same as that of unexposed plant employees.

There are various reports of asthma and related respiratory effects in pot room workers in the primary aluminum smelting industry. Exposure to fluoride (among other materials such as sulfur trioxide and polycyclic aromatic hydrocarbons) was measured as a possible index of exposures related to this condition (Seixas *et al*., 2000). However, multiple exposures to respiratory irritants and other compounds which may affect immune response appear to be common in this work environment making it difficult to quantitatively relate the respiratory symptoms to inhaled HF or fluorides.

Workers in a warehouse containing HF retorts experienced transitory hyperemia of the skin on their face and hands (Dale and McCauley, 1948). Twenty four of the 40 workers had definite changes in the thickness and number of trabeculae in the upper and lower jaw.

Examinations of 107 pot room workers in two aluminum plants with airborne fluorides revealed 22 subjects with limited motion of the dorsolumbar spine, compared with none in a control group of 108 workers with no history of exposure to fluorides (Kaltreider *et al.*, 1972). In one plant, 76 of 79 workers had increased bone density as measured by roentgenogram, with diagnosis of slight to moderate fluorosis. Moderate and marked fluorosis was observed after 15 years employment. The 8-hour time-weighted average fluoride content in these workplaces was 2.4 to 6.0 mg/m^3. Balazova (1971) measured significant fluoride uptake and distribution in children living near an aluminum smelter but reported no incidence of fluorosis.

No studies regarding the chronic irritant or respiratory effects of pure HF exposure in humans were available.

Fluoride ion produced by various fluorocarbons has been associated with toxicity to human kidney collecting duct cells leading to sodium and water disturbances (Cittanova *et al*., 1996).

Oral supplementation of greater than 0.1 mg F/kg body weight daily has been associated with enamel fluorosis in young children (Forsman, 1977).

The Agency for Toxic Substances and Disease Registry (ATSDR, 2001) recently reviewed fluorides since they are found at hazardous waste sites which are candidates for remediation. The focus of this document was on oral exposure studies as that is the main concern for waste site remediation.

V. Effects of Chronic Exposures to Animals

Stokinger (1949) studied the subchronic effects of HF inhalation in several animal species. Animals (dogs, rabbits, rats, guinea pigs, and mice; 1 to 6 per group) were exposed to 0, 7.2 mg/m^3, or 25.1 mg/m^3 6 hours/day, 6 days/week, for 30 days. Mortality, body weight, blood coagulation mechanisms, and gross pathology were measured. Exposure to 25.1 mg/m^3 HF for 30 days resulted in degenerative testicular changes and ulceration of the scrotum in all 4 dogs and hemorrhage and edema in the lungs of 3 dogs. Pulmonary hemorrhage was also seen in 20 of 30 rats, and 4 of 10 rabbits. Renal cortical degeneration was observed in 27 of 30 rats. All of the rats and mice at the 25.1 mg/m^3 concentration died. No mortality was observed in the other species tested. Blood fibrinogen levels were significantly increased in dogs, rats, and rabbits exposed to 25.1 mg/m^3. Exposure to 7.2 mg/m^3 HF resulted in pulmonary hemorrhage in 1 out of 5 dogs. No other significant effects were observed at the lower concentration.

Shusheela and Kumar (1991) administered male rabbits 10 mg NaF/kg-bw per day orally for 18 months (7 rabbits) or 29 months (3 rabbits), then studied the testis, epididymis, and vas deferens microscopically. After 29 months of F administration, the spermatogenic cells in the seminiferous tubules had degenerated and lacked spermatozoa. After both 18 and 29 months, cilia were lost from the epithelial cells lining the ductuli efferentes of the caput epididymidis. Stereocilia on the epithelial cells lining the vas deferens were also lost. In some regions of

epithelia, the cell boundaries were not clear, and even appeared to be peeled off. Mucus droplets were abundant in the vas deferens of controls, but none were present in F treated rabbits. Spermatogenesis ceased sometime between 18 and 29 months. The authors concluded that ingestion of a high concentration of F has adverse effects (including infertility) on the male rabbit reproductive system.

Ghosh *et al*. (2002) investigated the effects of NaF on steroidogenic and gametogenic activities in rat testes. Male Wistar rats were given 20 mg/kg/day NaF by gavage for 29 days. F treatment resulted in significantly lower relative wet weight of the testis, prostate, and seminal vesicle, decreased testicular delta(5),3beta-hydroxysteroid dehydrogenase (HSD) and 17beta-HSD activities, and significant lowering in plasma levels of testosterone. Epididymal sperm count was decreased significantly in F-treated rabbits and there were fewer mature luminal spermatozoa. Indicators of oxidative stress due to F included increased conjugated dienes in the testis, epididymis, and epididymal sperm pellet, and decreases of peroxidase and catalase in the sperm pellet. Thus F, at a dose encountered in drinking water in contaminated areas (at least of India), exerts an adverse effect on the male rat reproductive system. These effects on rats and rabbits (and dogs; see above) may be relevant to anecdotal reports of reproductive system malfunction in human chronic fluorosis.

Parameter	Control (n=6)	NaF (n=6)	p value
Body weight, final (g)	127.00±3.75	122.00±5.10	
Testis, relative weight (%)	1.522±0.034	1.923±0.081	< 0.05
Prostate, relative weight	0.297±0.043	0.148±0.014	< 0.05
Seminal vesicles, rel. weight	0.448±0.025	0.174±0.027	< 0.05
Testicular delta(5),3beta HSD	~28[a]	~24[a]	< 0.05[b]
Testicular 17betaHSD	~29[a]	~24[a]	< 0.05[b]
Plasma testosterone (ng/ml)	~2[a]	~1[a]	< 0.05[b]
Epididymal sperm count (10^6/ml)	7.02±0.17	3.70±0.57	< 0.05

[a] approximate values based on reading Figures 2 and 3 of paper; [b] p values of authors

Long *et al*. (2002) used ligand binding and Western blotting to study neuronal nicotinic acetylcholine receptors (nAChRs) in the brains of male and female Wistar rats ingesting 0.5 ppm (controls), 30 ppm, or 100 ppm F in their drinking water for 7 months. (All received 4 ppm F in their diet.) The brains of rats exposed to 100 ppm had significantly less binding sites for [^{3}H]epibatidine, an analgesic agonist, but no change occurred at 30 ppm. Binding sites for [^{125}I]alpha-bungarotoxin, a competitive antagonist, were significantly decreased in the brains of rats exposed to both levels. The brain levels of the nAChR alpha4 subunit protein was significantly lowered by exposure to 100 ppm F. Alpha7 subunit protein was significantly decreased by both levels of F. No significant changes were seen in levels of the beta2 subunit protein. These nicotinic receptors have roles in learning and memory. Some of the effects were also seen in rat PC cells cultured for 48 h in up to 50 ppm F (Chen *et al*., 2003). The results may help to explain anecdotal reports of nervous system symptoms in human chronic fluorosis (Waldbott, 1978).

NTP (1990) exposed F344/N rats and B6C3F1 mice of both sexes for two years to 0, 25, 100, and 175 ppm sodium fluoride (NaF) in their drinking water. NaF caused a dose dependent

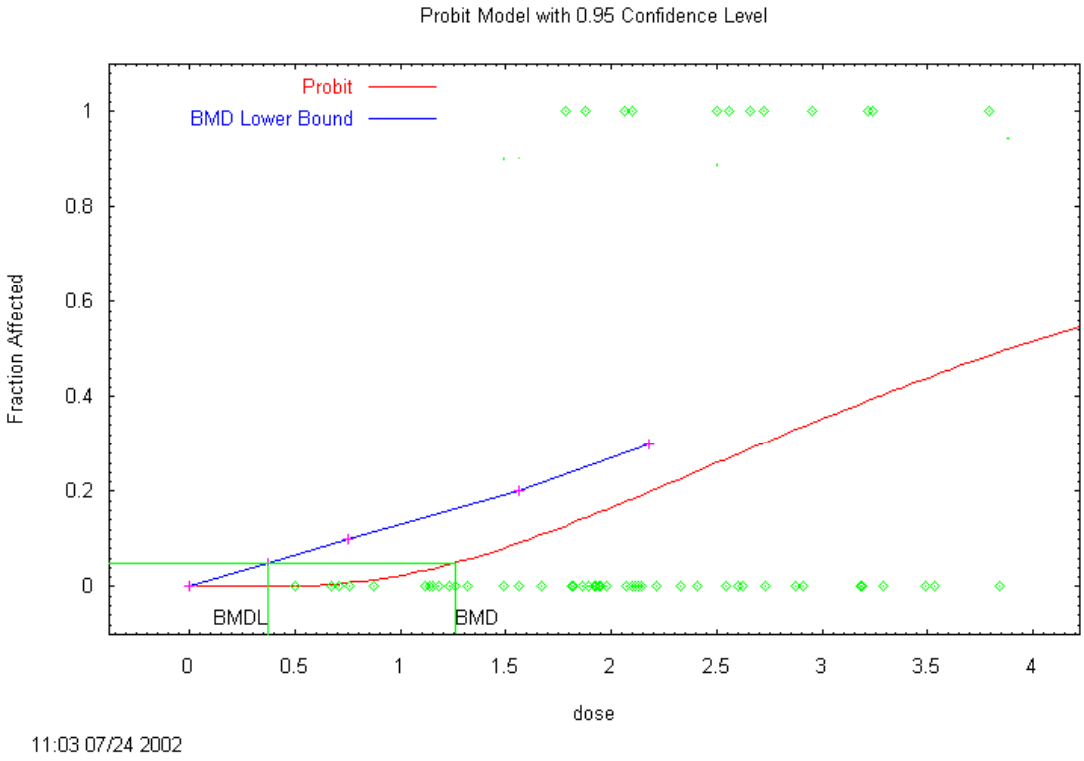
whitish discoloration of the teeth in both rats and mice. Male rats had an increased incidence of tooth deformities and attrition. NaF increased the dysplasia of dentine in both rats and mice. At the highest dose (175 ppm), osteosclerosis of long bones was increased in female rats. There was also equivocal evidence of carcinogenic activity of NaF in male rats based on four osteosarcomas in dosed animals (Bucher *et al*., 1991). Other organ systems showed no dose-dependent effects.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Derryberry *et al.* (1963)
Study population	74 fertilizer plant workers (67 unexposed control subjects)
Exposure method	Occupational
Critical effects	Increased bone density (skeletal fluorosis)
LOAEL	1.89 mg F/m^3 (1.98 mg HF/m^3)
NOAEL	1.07 mg F/m^3 (1.13 mg HF/m^3)
BMC_{05}	0.37 mg F/m^3 (0.39 mg HF/m^3)
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	14.1 years (range = 4.5 to 25.9 years)
Average exposure concentration	0.14 mg HF/m^3 (0.39 x 10/20 x 5/7) or 0.13 mg F/m^3 (0.37 x 10/20 x 5/7)
Human equivalent concentration	0.14 mg HF/m^3 or 0.13 mg F/m^3
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference exposure level for F or HF	0.013 mg F/m^3 (13 μg /m^3; 0.016 ppm; 16 ppb) or 0.014 mg HF/m^3 (14 μg /m^3; 0.017 ppm; 17 ppb)

OEHHA's analysis of the data in Derryberry *et al*. (1963) indicates a LOAEL of 1.89 mg/m^3, and a NOAEL of 1.07 mg/m^3. A benchmark concentration (BMC_{05}) of 0.37 mg/m^3 was derived by fitting the probit model to the log dose in the U.S. EPA's BMDS (version 1.3) software, for the individual mean air exposure data and incidence data in Table 1 above. Individuals in the highest dose group (group 5 in Table 2) were not included in the model, since none of the models fit this range of exposures well. Several other models produced reasonable fits to the data, but the probit model with log-transformed dose was selected since it produced a good fit not only by statistical criteria ($p = 0.71$) but also, as determined by inspection, it fit the low dose curve shape better than other models. This model also has the advantage of biological plausibility, in that, since lower doses of fluoride have a beneficial or nutritional effect, a threshold type of response for adverse effects is clearly expected. A graphical representation of the fit is shown in Figure 1. Adjusting for exposure continuity and utilizing an intraspecies uncertainty factor of 10 (UF_H) results in a REL for F of 13 μg/m^3.

Figure 1.



Changes in bone density in association with fluoride exposure have been observed in several studies, and appear to be the most sensitive health effect for chronic exposure. The minimally increased bone density in the Derryberry study was significantly ($p < 0.04$, Fisher's Exact Test) associated with "other osseous changes," which reportedly included disc lesions, arthritis, and calcified ligaments. An increase in pulmonary changes in the workers with high bone density was marginally significant ($p < 0.06$) and included emphysema, fibrosis, and healed tuberculous lesions. Although dental fluorosis is a sensitive endpoint in many fluoride studies, the dental examinations of exposed workers in this study showed healthier teeth than in controls. The increased bone density observed was considered as indicating that adverse effects had occurred, based on the adverse effects associated with the increased density in the study, and on other research showing that increased bone density caused by fluoride exposure (75 mg sodium fluoride per day for four years) also leads to decreased bone strength and increased fragility (Riggs *et al.*, 1990). Symptoms of abdominal pain, backache, restricted joint movement, and respiratory symptoms have been associated with airborne fluoride exposures and bone density increases in industrial settings (Zhiliang *et al.*, 1987).

The absorption of particulate and gaseous fluorides is reported to be similar (Collings *et al.*, 1951). Therefore, it would be expected that the effects on bone density would be similar regardless of the form of fluoride.

As noted in the study description, Derryberry *et al.* (1963) did not find a good correlation between years of exposure to fluoride and bone density change. OEHHA reexamined the original individual data and confirmed that the presence of bone density changes showed a better correlation with mean air fluoride concentration than with years of exposure, or with the product of the individual values of mean air fluoride concentration and years of exposure. However, the product of exposure concentration and time did show a consistent pattern of cumulative incidence suggesting a dose-response relationship for this parameter. An attempt to derive a benchmark value by fitting the probit model to the log of (exposure duration*concentration) and response (presence or absence of bone density change) did not result in an acceptable fit, so a $BMDL_{05}$ could not be reported. However a maximum likelihood estimate of the benchmark (BMD_{05}) was found to be 6.04 (mg F*years/m^3), with exclusion of the three highest values that appeared to be outliers to the main distribution. If this value is divided by the mean exposure duration for the data set of 14.1 years, a benchmark exposure concentration of 0.43 mg F/m^3 is obtained. While this value is evidently less reliable than that obtained by fitting the mean exposure concentration, it is consistent with it, suggesting that, although other confounding factors related to age or duration prevent the demonstration of a relationship between the exposure/time integral and response in this data set, such a relationship probably does exist, as would be expected.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the key study for fluoride are the observation of health effects in a large group of workers exposed over many years, the availability of individual exposure estimates for each worker, and the identification of a NOAEL. The primary uncertainty in the study is the lack of a comprehensive health effects examination. Another source for concern is the potentially greater susceptibility of children to the effects of inhaled fluorides, considering the rapid bone growth in early years.

Derivation of Chronic Oral REL

In addition to being inhaled, airborne fluoride salts in particulate form can settle onto crops and soil and enter the body by ingestion. Thus an oral chronic reference exposure level (REL) for fluoride is also required in order to conduct a health risk assessment under the Air Toxics Hot Spots Act. California has developed a Public Health Goal (PHG) of 1 ppm (1,000 ppb) fluoride in drinking water (OEHHA, 1997). This level is intended to be an approximate year-round average. Thus it has properties similar to a chronic oral REL. (The PHG assumed that drinking water was the only source of fluoride since it was based on comparing communities with and without added fluoridation.)

Study	Dean, 1942; U.S. Public Health Service, 1991; National Research Council, 1993
Study population	Inhabitants of several U.S. cities
Exposure method	Drinking water
Critical effects	Dental fluorosis
LOAEL	2 ppm
NOAEL	1 ppm = 0.04 mg/kg-day*
Exposure continuity	Continuous
Exposure duration	Long-term
Average experimental exposure	1 ppm = 0.04 mg/kg-day
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1 (studies included children)
Cumulative uncertainty factor	1
Oral reference exposure level	0.04 mg/kg-day

* based on the assumption that an 18 kg child drinks 720 ml of water per day (OEHHA, 2000).

The PHG is based on a no-observed adverse-effect-level (NOAEL) of 1 mg/L for dental fluorosis in children (equivalent to 720 µg/day from drinking water for an 18 kg child drinking 40 ml/kg body weight/day of water). Moderate to severe dental fluorosis is rare when the drinking water fluoride level is near 1 mg/L, but begins to become significant at concentrations close to 2 mg/L. Since the study involved long term exposure to humans including children, a sensitive population, the cumulative uncertainty factor was 1. If one were to do a route-to-route extrapolation from this oral REL using the specific parameters for an 18 kg child breathing 4.2 m^3/day, an equivalent inhalation REL would be about 170 µg/m^3. Thus, the inhalation REL of 13 µg/m^3 based on the adult occupational data is likely to be protective of children.

VIII. Potential for Differential Impacts on Children's Health

The critical effect for inhalation exposures is skeletal fluorosis. Since infants' and children's skeletons are developing, they may be more sensitive to this effect. This applies with particular importance to the teeth, and it is established that excessive exposure to fluoride during the period of tooth development in infancy and childhood causes dental fluorosis (Dean, 1942; U.S. Public Health Service, 1991; NRC, 1993). The oral REL and the California PHG for fluoride in drinking water are based on dental fluorosis. Although the inhalation chronic REL proposed is based on a study in adults, the inhalation chronic REL (see section VI) is lower than that implied by the oral REL and PHG. Since the oral REL and PHG are based on exposures throughout life, including the pre-natal period, infancy, and childhood, it is reasonable to conclude that the proposed inhalation REL is generally protective of infants and children, barring some unknown difference in toxicity between the two routes of exposure. The ratio of the intake at the PHG level in drinking water is closer to the effect level than the default intraspecies uncertainty factor of 10; this is to be expected since children are a sensitive subpopulation for the dental fluorosis effect.

Extensive interindividual variation in total fluoride intake (930.7 ± 391.5 µg/day) was recently documented for a small group (n = 11) of healthy German children ages 3 to 6 years (Haftenberger *et al*., 2001). Similar interindividual variation has also been reported for slightly younger children in Connersville (n = 14) and Indianapolis, Indiana (n = 29) and in San Juan, Puerto Rico (n = 11) (Rojas-Sanchez *et al*., 1999). Consideration should therefore be given to populations with exceptionally high fluoride intake due to locally elevated concentrations in drinking water, since some of these populations are already close to adverse effect levels of fluoride intake, and certain individuals in California experience dental fluorosis. For these individuals, even exposure to fluorides at the oral and/or inhalation RELs, which are acceptable in isolation, might be deleterious. The table below compares the data of Haftenberger *et al*. (2001) with recent estimates of F intake ranges in California (OEHHA, 1997).

Fluoride Intake (mg/day)

F in drinking water (mg/L)	F from drinking water	F from food	F from toothpaste	F from mouthwash	F from a supplement	Total F
Children (OEHHA)						
<0.3	0.1 - 0.3	0.1 – 0.5	0.2 – 1.2	0.1 - 0.5	0.5	1.0 – 3.0
0.7 - 1.2	0.7 - 1.2		0.2 – 1.2	0.1 - 0.5	0	1.1 – 4.6
Haftenberger						
0.25	(see food)	0.20±0.12	0.27±0.18	No data	0 - 1.0	0.93±0.39
Adults (OEHHA)						
<0.3	0.2 – 0.6	0.3 – 1.0	0.02 – 0.15	0.2 – 1.0	0	0.7 – 2.8
0.7 - 1.2	1.4 – 2.4	0.3 – 3.4	0.02 – 0.15	0.2 – 1.0	0	1.9 – 7.0

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